

Radionuclide left ventricular ejection fraction: a comparison of three methods

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SUMMARY Three commercially available computer programs (a semiautomatic method, a manual method, and a regional method) were used to calculate left ventricular ejection fraction from the equilibrium multiple gated radionuclide ventriculograms obtained from 24 normal male subjects and 20 men with heart failure. In the normal subjects the ejection fraction values calculated by each method were significantly different (mean (SD) difference between semiautomatic and manual 3.3 (5.8); between semiautomatic and regional 12.0 (6.3); and between manual and regional 8.7 (6.9)). In the patients with heart failure the ejection fraction values calculated by the semiautomatic method differed significantly from those calculated by the manual and regional methods (mean (SD) difference between semiautomatic and manual 3.4 (4.7); between semiautomatic and regional 4.9 (4.9); and between manual and regional 1.5 (6.2)). The ejection fraction values obtained by the semiautomatic method were generally higher and more consistent than those derived from the manual and regional methods. An ejection fraction of $\geq 50\%$ with the semiautomatic method would be regarded as normal but if the same normal range was applied to the regional method nine (38%) of the 24 normal subjects would appear to have an abnormal left ventricular function.

Clinicians should be aware that the method used to generate a time-activity curve is an important consideration in the calculation of ejection fraction. Each centre should establish its own range and reproducibility for the method it uses to measure ejection fraction. These values should not be assumed to apply to any other method.

Since the first descriptions of the use of radionuclide techniques to measure left ventricular ejection fraction^{1,2} and to detect regional ventricular dysfunction,³ radionuclide ventriculography has become increasingly important not only to the management of patients with cardiac disease but also to the investigation of patients in various physiological states and during pharmacological intervention. The technique is safe, repeatable, and does not induce measurable alterations in haemodynamic function.⁴ Initially, manual methods were used to calculate the ejection fraction from the radionuclide scan with the observer tracing the ventricular mar-

gin in end diastole and end systole; many centres still use this method. Improved computer technology has produced automated techniques for tracing the ventricular contour, these techniques relying on edge defining algorithms to detect the ventricular margin. Automated techniques are claimed to give more consistent results⁵; however, some believe that edge defining algorithms are liable to error and they still favour the manual method for selecting regions of interest.⁶ Automation has increased the number of companies marketing programs and the number of programs available to calculate ejection fraction. These programs differ in the way in which they generate a time-activity curve and it is apparent that this may lead to differences in ejection fraction values between programs.

The purpose of this study was to investigate the differences between three commercially available

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methods used to calculate ventricular ejection fraction and to assess the variability of these methods.

Patients and methods

The multiple gated radionuclide ventriculograms of 24 normal men and 20 men with heart failure were studied retrospectively. All the normal subjects had no history of cardiac disease, normal cardiovascular examination, and a normal electrocardiogram. Ischaemic heart disease was the cause of heart failure in 18 patients, with alcoholic cardiomyopathy and cardiomyopathy of unknown cause being the primary diagnoses in the other two patients.

Red blood cells were labelled *in vivo* by an intravenous injection of 10 mg unlabelled stannous pyrophosphate followed 20 minutes later by 740 mBq of technetium-99m. Multiple gated ventriculograms were obtained by means of an Anger scintillation camera with a low energy, all purpose collimator (Elsint, Apex 215M). The camera was positioned in the 30°–45° left anterior oblique projection with 5°–10° caudal tilt in order to isolate the left ventricle. The R-R interval was divided into 32 frames and a 5% gate tolerance was used. Five million counts were collected and the data were stored on a 64 × 64 matrix to obtain a high resolution time-activity curve of the change in precordial radioactivity.

Three commercially available programs that are widely used in different centres were used to measure the left ventricular ejection fraction from the ventriculogram—a semiautomatic method,⁷ a manual method, and a regional method⁸ that estimates the ejection fraction of the lateral, inferoapical, and septal regions as well as the global ejection fraction. The same time correction and nine point smoothing was applied to every scan studied by each method. To correct for non-cardiac activity the same background region of interest was used with each method; this region was two pixels wide and two pixels from the left lower quadrant of the left ventricle on the end systolic frame. The method used to generate a time-activity curve was different with each program. With the semiautomatic method the observer drew a region of interest around the ventricle on the first frame. A second derivative edge-defining algorithm automatically determined the ventricular outline of all frames of the cycle. If necessary the observer could alter the outline of any frame. With the manual method the observer traced the outline of the ventricle on the first frame and the end systolic frame. With the regional method the observer drew a region of interest around the ventricle on the first frame and a second derivative edge-defining algorithm was used to determine the ventricular outline in this frame, the outline being

altered by the observer if necessary. This outline was then positioned on all 32 frames.

One observer (observer 1) estimated the ejection fraction in all subjects using each program on two separate occasions. The intraobserver variability was estimated from the results of the 24 normal subjects only. The mean of the two ejection fraction readings was used to analyse the differences between the programs. Two other observers (observers 2 and 3) estimated the ejection fraction in 10 of the 24 normal subjects using each program on one occasion. Their results were compared with the first estimation by observer 1 in the same 10 subjects to estimate the interobserver variability for each program.

Student's *t* tests (two tailed) were used to estimate the intraobserver variability. Two way analysis of variance was used to estimate the interobserver variability and the differences between the three programs. A difference was regarded as significant when $p < 0.05$.

Results

The mean age of the 24 normal subjects was 37 years (range 20–58) and that of the 20 patients with heart failure was 61 years (range 47–74). The mean ejection fraction (SD) in the 24 normal subjects was 63 (6.9)% (range 51–78%) for the semiautomatic method, 60 (6.3)% (range 46–70%) for the manual method, and 51 (8.2)% (range 35–66%) for the regional method. In the 20 patients with heart failure the mean ejection fractions were 29 (9.4)% (range 14–45%), 26 (9.4)% (range 13–46%), and 24 (5.9)% (range 17–38%) for semiautomatic, manual, and regional methods respectively.

INTRAOBSERVER AND INTEROBSERVER VARIABILITY

A comparison of the first and second ejection fraction values obtained by each method in both groups (table 1) showed no significant intraobserver variability in either group with any of the methods. The comparison of the readings obtained by three observers using each method in 10 of the 24 normal subjects (tables 2 and 3) showed no significant interobserver variability. Comparison of the intraobserver and interobserver variability in the normal subjects (table 4), however, showed that the interobserver variability was significantly greater than the intraobserver variability with the manual and regional methods ($p < 0.05$ and $p < 0.025$ respectively) but not with the semiautomatic method ($p = \text{NS}$).

COMPARISON OF PROGRAMS

We compared the three programs in both groups of

Table 1 Comparison of the first and second ejection fraction (EF) values obtained by each method in the normal subjects and subjects with heart failure

Method used to measure EF	Mean difference	SE of mean difference	p value
Normal:			
Semiautomatic	-0.29	0.61	NS
Manual	-0.13	0.75	NS
Regional	+0.88	0.76	NS
Heart failure:			
Semiautomatic	+0.20	0.50	NS
Manual	+1.40	0.80	NS
Regional	-0.60	0.61	NS

Table 2 Comparison of ejection fraction (EF) values obtained by observers 1 and 2 in 10 normal subjects

Method used to measure EF	Mean difference	SE of mean difference	p value
Semiautomatic	-1.2	1.16	NS
Manual	-2.0	2.01	NS
Regional	-2.4	1.96	NS

Table 3 Comparison of ejection fraction (EF) values obtained by observers 1 and 3 in 10 normal subjects

Method used to measure EF	Mean difference	SE of mean difference	p value
Semiautomatic	-1.8	1.31	NS
Manual	-0.9	1.35	NS
Regional	-1.8	2.11	NS

subjects by plotting the average of the mean ejection fraction obtained by any two programs against their difference.⁹ In the normal subjects (fig 1) the mean difference (SD) between the semiautomatic and manual methods was 3.3 (5.8)% ($p < 0.02$), between the semiautomatic and regional methods it was 12.0 (6.3)% ($p < 0.0001$), and between the manual and regional methods it was 8.7 (6.9)% ($p < 0.0001$). There was no correlation between the average ejection fraction and the difference for any of the comparisons, indicating that the difference was not related to the magnitude of the ejection fraction. As shown on the histograms of the distribution of differences, the ejection fractions obtained from the

semiautomatic method were generally higher than those from the other two methods; the ejection fractions obtained from the regional method were appreciably lower than the semiautomatic and manual methods. In the patients with heart failure (fig 2) the mean (SD) difference between the semiautomatic and manual methods was 3.4 (4.7) ($p < 0.01$), between the semiautomatic and regional methods it was 4.9 (4.9) ($p < 0.0005$), and between the manual and regional methods it was 1.5 (6.2) ($p = \text{NS}$). There was no correlation between the average ejection fraction and the difference when the semiautomatic and manual methods were compared but there was a positive correlation for the comparison of semiautomatic and regional methods ($r = 0.75$, $p < 0.0002$) and manual and regional methods ($r = 0.60$, $p < 0.005$). Again the ejection fraction values obtained with the semiautomatic method were generally higher than those obtained with the manual and regional methods.

Discussion

We have compared three commercially available programs that are used for the estimation of ejection fraction and we have demonstrated that the method used to generate a time-activity curve is an important consideration in the calculation of ejection fraction. Throughout the whole range of ejection fraction values the semiautomatic method gave significantly higher values than the manual and regional methods. The semiautomatic method also produced more consistent results than the other two methods with which the interobserver variability was significantly greater than the intraobserver variability. However, our results with the manual method do not support the view of Reiber *et al* that the manual method is characterised by large interobserver and intraobserver variations.⁵

There are important differences between the three programs in the method of generating a time-activity curve. With the manual method the first frame is assumed to be the end diastolic frame. The end diastolic frame is sometimes at a different point in the cycle, however, and this would lead to an underestimation of the end diastolic counts and,

Table 4 Comparison of intraobserver and interobserver variability in ejection fraction in normal subjects

Method used to measure EF	SD of differences between 2 EF values obtained by observer 1 (SD_1)	SD of differences in EF values obtained by 3 observers (SD_2)	Ratio of variance (SD_2^2/SD_1^2)	p value
Semiautomatic	3.00	3.71	1.53	NS
Manual	3.69	5.51	2.23	<0.05
Regional	3.71	6.21	2.80	<0.025

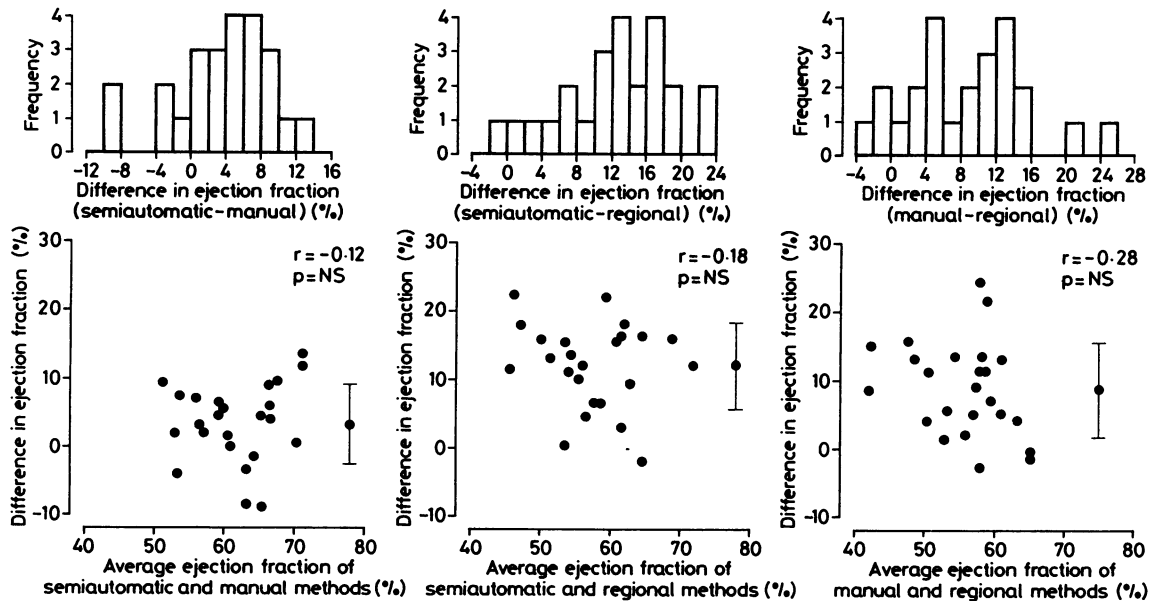


Fig 1 Comparisons of the mean ejection fraction values obtained with each method in 24 normal subjects. The mean difference ± 1 SD is shown for each comparison.

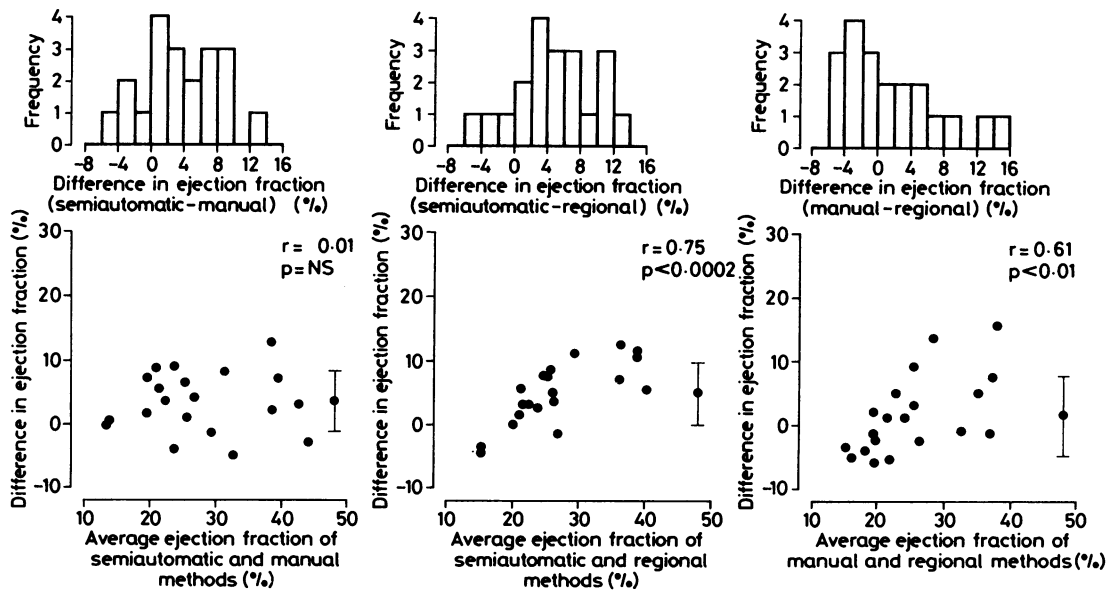


Fig 2 Comparisons of the mean ejection fraction values obtained with each method in 20 patients with heart failure. The mean difference ± 1 SD is shown for each comparison.

therefore, of the ejection fraction. Because the semiautomatic method defines the ventricular margin in all 32 frames it identifies the end diastolic frame more accurately. We believe that this difference in identifying the end diastolic frame accounts for the differences observed between these two methods. The regional method used transfers the left ventricular margin from the first frame on to all the frames in the cycle. Again the assumption that the first frame is the end diastolic frame could lead to an underestimation of the ejection fraction. Furthermore, by superimposing the left ventricular margin from the first frame on to all frames the counts from the end systolic frame will include extracardiac counts and this will lead to further underestimation of the ejection fraction. At low ejection fractions the effect of the extracardiac counts will be less because the end diastolic left ventricular margin will approximate the end systolic left ventricular margin; as the ejection fraction increases the extracardiac counts increase and this approximation becomes less. It is this factor that accounts for the positive correlation between the average ejection fractions and the differences between methods when the regional method is compared with the semiautomatic and manual methods in the patients with heart failure. In our centre the normal range of ejection fraction established with the semiautomatic methods was $\geq 50\%$. If this normal range was applied to the regional method nine (38%) of the 24 normal subjects would be regarded as having abnormal cardiac function.

Although the semiautomatic method produces the most consistent results it is difficult to prove that it produces the most accurate results. Cardiac phantoms have been used to determine the most accurate methods but there are large differences between the quoted and estimated ejection fraction.⁶ The verification of programs remains a problem; until it is solved unsatisfactory programs will continue to be marketed and comparison between different centres will remain difficult. Because the time-activity curve is now being used to calculate various indices of ventricular systolic and diastolic function the issue of quality control becomes even more important. It has been suggested that quality control of the analysis software is best done by means of a library of patient data, the results of which have been previously authenticated.⁶ However, as was acknowledged, if the data were collected on another system the prob-

lem of data transfer and compatibility becomes a major issue.

Clinicians should be aware that the measurement of ejection fraction is dependent on the method used and each centre should establish its own normal range and reproducibility for the method it uses to measure the ejection fraction and should not assume that these values will apply to any other method or even to the same method produced by another company.

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